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OPHTHALMIC IN-SITU DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Ocular drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists, the major problem encountered to pharmaceutical scientist is rapid precorneal elimination of the drug, resulting in poor bioavailability and therapeutic response, because of high tear fluid turnover and dynamics. This problem can be overcome by using in situ gel forming ocular drug delivery system, prepared from polymer, exhibit sol-to-gel phase transition due to a change in a specific physio-chemical parameter (pH, temperature, ion-sensitive).In situ gels are conveniently dropped as a solution into the conjunctival sac, where they undergo a transition into a gel with its favorable residence time. The sol-gel transition occurs as a result of a chemical/physical change induced by physiological environment. This type of gel combines the advantage of a solution (accurate and reproducible administration of drug) and gels (prolong residence time) for improving occular bioavailability. This review is to specify the different phase transition process and polymers used in forming in-situ gelling system.

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INTRODUCTION

Conventional ophthalmic delivery systems like eye drops result in poor ocular drug bioavailability due to ocular anatomical and physiological constraints, which include the relative impermeability of the corneal epithelial membrane, tear dynamics and nasolacrimal drainage. Most of the topically applied drugs are washed off from the eye by various mechanisms include lacrimation, tear dilution and the residence time of most conventional ocular solutions ranges between 5 and 25 minutes. Only 1-10% of topically applied drug is absorbed, and major part of drug absorbed systemically results in systemic side effects.[1,2]

A significant increase in the precorneal residence time of drug and consequently better bioavailability can be achieved by using delivery system based on the concept of in situ gel formation. These in situ gelling systems consist of polymer that exhibit sol-to-gel phase transitions

due to change in specific physicochemical parameters (pH, Temperature, ionic strength) in the environment, cul-de-sac in the case of eye. The sol-to-gel phase transition on the eye surface depending on the different methods employed and they are: pH-triggered system (eg.Cellulose acetate hydrogen phthalate latex), temperature dependent system (eg.Pluronics and tetronics) and ion activated system (eg.Gelrite). Many of the ophthalmic in situ forming gels investigated to date have been formulated with carbomers or cellulose derivatives [3].

Various different preparations like ocular inserts, hydrogel etc have been developed to prolong the contact time on ocular surface. The main problem with these preparations is patient compliance and blurred vision [4], so that the liquid dosage forms are more preferable.

An ideal ocular preparation must be:

1) That on instillation does not cause any irritation to the eye and blurred vision.

2) Able to withstand lacrimal fluid dilution without being rapidly eliminated after the instillation by precorneal elimination.

3) Should have retaining power so that the drug remain in the precorneal area for longer period of time and increase the bioavaibility of drug in the eye.[4]

To overcome the problem of conventional dosage form i.e. rapid drug loss blurred vision and patient incompliance, so in-situ gels can be prepared.

ANATOMY OF HUMAN EYE:[5,6,7]

The eye is a small but complex organ in the human body. Its orbit shape is maintained by the clear jelly-like substance within called the vitreous. The eye is supported by muscles which control the movement of the eye, open and close the eyelid, turn and roll the eye. It is protected by a tough outer layer called the sclera. The sclera is typically white, but can be discolored in the presence of certain diseases. The eyes work in conjunction with the brain. As light enters the eye, electrical signals are sent to the brain and images are formed. Each eye sees something slightly differently and, by putting the two views together, the brain forms three-dimensional images. It functions much like a camera. The eye is regularly bathed in tears, every time we blink. Tears protect the eye, washing away dirt and dust, and killing bacteria. The anatomy of the eye is made up of a number of parts which work together to relay information to the brain.

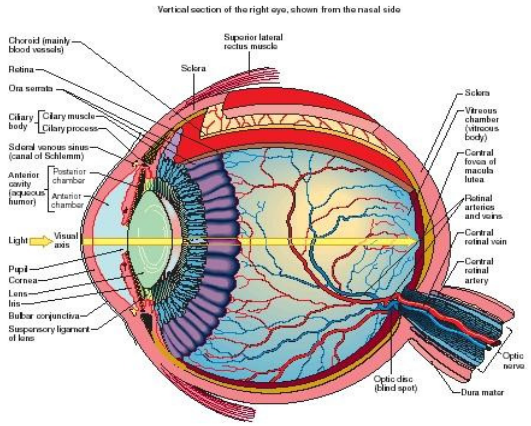

Fig: 1- Anatomy of Human Eye.

1) Extra ocular Structures:

The eye is protected by the eyelids and by the orbit, a bony cavity of the skull that has multiple fissures and foramina that conduct nerves, muscles, and vessels. In the orbit, connective (i.e.Tennon's capsule) and adipose tissues and six extra ocular muscles support and align the eyes for vision. The retro bulbar region lies immediately behind the eye (or globe). Understanding ocular and orbital anatomy is important for safe periocular drug delivery, including subconjunctival, sub-Tenon's and retrobulbar injections.

2) Ocular Structure:

1. Cornea: The transparent, curved outer surface of the eye is the cornea. It is composed of five layers, primarily water and collagen. It lets light into the eye and covers the iris. It contains no blood vessels and remains clear when the eye is in good health.

2. Iris: The iris is the visible colored part of the eye and extends anteriorly from the ciliary body, lying behind the cornea and in front of the lens. It divides the anterior segment of the eye into anterior and posterior chambers which contain aqueous fluid secreted by the ciliary body. It is a circular body composed of pigment cells and two layers of smooth muscle fibres, one circular and the other radiating. In the centre there is an aperture called the pupil.

3. Lens: The lens is a highly elastic circular biconvex body, lying immediately behind the pupil. It consists of fibres enclosed within a capsule and it is suspended from the ciliary body by the suspensory ligament. Its thickness is controlled by the ciliary muscle through the suspensory ligament. When the ciliary muscle contract, it moves forward, increasing its thickness. The nearer is the object being viewed, the thicker the lens becomes to allow focusing.

4. Retina: The retina is the innermost layer of the wall of the eye. The back of the eye is lined by a layer of nerve tissue that contains photoreceptors; there are about 125 million rods and 6 million cones. At the centre of the retina, within the macula, is the fovea, the area of sharpest vision. It captures the light reflected by the lens converting it to electrical impulses that are passed to the brain.

5. Macula: Within the retina, at approximately the centre, is the macula. It absorbs excess light and is responsible for sharp central vision, allowing us to see fine print. It converts the light into nerve signals via the photoreceptors within the fovea at its centre.

6. Optic Nerve: The fibres of the optic nerve originate in the retina and they coverage to form the optic nerve about 0.5 cm to the small nasal side of the macula lutea. The nerve pierces the choroid and sclera to pass backwards and immediately through the orbital cavity.

7. Conjunctiva: This is a fine transparent membrane that lines the eyelids and the front of the eye ball. Where it lines the eyelids consists of highly vascular columnar epithelium, i.e. epithelium without blood vessels. When eyelids are closed the conjunctiva becomes a closed sac. It protect the delicate cornea and front of the eye. When eye drop are administered they are placed in the lower conjunctival sac.

DRUG DELIVERY SYSTEM FOR THE EYE:

The most common route for treatment of ocular disease is topical medication**.** The application of drug via this route is preferred due to ease of application and low cost. Topical route for the application is used for the treatment of disorder affecting the anterior segment of the eye. The various anatomical and physiological barriers are there which hinders the drug absorption to the posterior segment of eye. A major fraction of applied drug formulation is loss due to nasolachrimal drainage and high ratio of tear turn over which causes lower bioavaibility of drug to posterior part of eye.

The route of administration is mainly depending on permeability of drug molecule. Other routes are also there for treatment of disease which includes systemic and intra-ocular route. Systemic route is mainly used for the treatment of disease affecting posterior part of eye. The main drawback of systemic route is avaibility of drug which is 1-2% which reaches to vitreous humor. The main barrier in this route is blood retinal barrier which governs the entry of drug to posterior segment of eye. The intra-ocular route of administration includes intravitreal delivery of drug to posterior part of eye. [8,9].

MECHANISM OF OCULAR ABSORPTION: [10, 11, 12]

The drug from the eye is absorbed by the two routes i.e. by corneal route and non corneal route

Corneal route

The corneal absorption is the major pathway of drug absorption for topically applied formulation. The drug absorption is occurring by two mechanism transcellular and paracellular diffusion. Most of the lipophilic drugs are absorbed by transcellular diffusion and hydrophilic drugs are absorbed by paracellular diffusion. In general, corneal penetration is governed by the lipophilicity of drug but it also affected by other factors including solubility, molecular size and shape, charge and degree of ionization.

Non-corneal route

The absorption is occurring through conjunctiva and sclera. There are three routes by which drug can penetrate through sclera.

a) Through the perivascular spaces.

b) Through the aqueous media of gel like mucopolysaccharides.

c) Through the empty spaces within collagen network.

This route is considered as non productive route as most of the drug reaches to the systemic circulation before it reaches to the intraocular tissues this route may be important for the hydrophilic compounds with large molecular weight compound like timolol maleate and gentamycin.

METHOD BY WHICH PHASE TRANSITION CAN OCCURS:

There are three methods which are used to trigger the phase change at ocular surfaces

a) Transition by change in temperature

b) Transition by change in pH

c) Transition by change in electrolyte composition

a) Transition by change in temperature [10, 13,14,15,16]

These in situ gels are liquid at room temperature (20-25^0) and when they come in contact with fluid present in the eye (35-37^{0}c) they undergo phase transition as temperature increases. The polymers used for temperature induce gelation include poloxamer, cellulose derivative and xyloglucan.

Three main strategies exist in engineering of thermo responsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogel are classified into negatively thermo sensitive, positively thermo sensitive and thermally reversible gels. Negative temperature-sensitive hydrogel have a lower critical solution temperature (LCST) and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature is used for this purpose. one of the most extensively investigated polymers that exhibit useful LCST transition is poly(Nisopropylacrylamide) (PNIPAAm). PNIPAAm is a water soluble polymer at its low LCST, but hydrophobic above LCST, which result on precipitation of PNIPAAm from the solution at the LCST. Platonic's are poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPOPEO) triblock co-polymer that are fluid at low temperature, but forms thermo responsible gel when heated as a consequences of a disorder-order transition in micelle packing which makes these polymers suitable for in situ gelation. A positive temperature sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate) have positive temperature dependence of swelling. The most commonly used thermoreversible gels are these prepared from poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (Pluronics®, Tetronics®, poloxamer).

Poloxamers are thermo reversible phase change polymers which consist more than 30 different non-ionic surface active agents. These contain a tri-block of A-B-A type having polyethylene dioxide (PEO) polypropylene dioxide (PPO). The PEO-PPO-PEO unit is commonly known as pluronics. It is available as liquid, paste and solid due to different molecular weight of PEO-PPO unit. The poloxamer are liquid below 25^{0}C and goes thermogellation between 25 to 30^{0}C and thus increases the residence time on ocular surface.

b) Transition by change in pH [10, 16]

In these gels the transition of the phase is triggered by change in pH. The polymers used are cellulose acetate phthalate (CAP), latex and its derivatives like carbomers. The CAP is free flowing liquid solution at pH 4.2 and it becomes gel at pH 7.2 for this property it is widely used in making ophthalmic in-situ gel.

Carbomers which is cross linked poly (acrylic acid) and high weight molecular polymer commonly known as carbomer are widely used in ophthalmic preparations.

All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH .The polymers with a large number of ionisable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The most of anionic pH-sensitive

polymers are based on PAA (Carbopol®, carbomer) or its derivatives.

c) Transition by change in electrolyte composition

In this the phase transition from sol to gel is triggered by change in ionic strength. The most common polymer used for ion sensitive in situ gel are gellan gum i.e. gelrite which is a heteropolysaccharide secreted by microbe sphingomonas erodea.The gelrite consist of glucose, glucouronic acid and rhamnose in a molar ratio 2:1:1.

Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na+. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca2+. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca2+ due to the interaction with guluronic acid block in alginate chains.

Importance of in situ gelling system

The major importance is the possibility of administering accurate and reproducible quantities compare to already formed gel. It is conveniently dropped as solution into the conjunctival sac, enhancing patient compliance and minimizing interference with blinking. It increases the contact time of drug with the mucus at the site of absorption and has better bioavailability [18].

These systems have the advantages:

- Prolonged drug release
- Reduced systemic side effects
- Reduced number of applications
- Better patient compliance.
- Generally more comfortable than insoluble or soluble insertion.
- Less blurred vision as compared to ointment.

EVALUATION AND CHARACTERIZATION OF IN SITU GELLING SYSTEM:

Clarity:

The clarity of formulated solution is determined by visual inspection under black & white background.[19]

Texture analysis:

The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringeability of sol so the formulation can be easily administered in-vivo. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surfaces like tissues.[20].

pH OF GEL:

pH can be determined formulation is taken in beaker & 1ml NaOH added drop wise with continuous stirring. pH is checked by using pH meter.[21]

Sol-Gel transition temperature and gelling time:

For in situ gel forming systems incorporating thermo reversible polymers, the sol-gel transition temperature may be defined as that temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the time for first detection of gelation as defined above.

Gelling capacity:

The prepared in situ gelling system was evaluated for gelling capacity in order to identify the composition suitable for use as in situ gelling system. The in situ gelling system was mixed with simulated tear fluid (in the proportion of 25:7 i.e. application volume 25µl and normal volume of tear fluid in the eye is 7µl) to find out the gelling capacity of the ophthalmic product. The gelation was then assessed visually by noting the time for the gelation and the time taken for dissolution of the formed gel.[22]

Drug content:

Uniform distribution of active ingredient is important to achieve dose uniformity. The drug content was determined by diluting 1 ml of the formulation to 100 ml with ATF solution pH 7.4. Aliquot of 1 ml was withdrawn and further diluted to 10 ml with ATF. Drug concentration were then determined by simultaneous method by using UV-Visible spectrophotometer.[23].

Rheological studies:

The viscosity measured by using Brookfield viscometer, cone & plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity 5-1000 mPas , before gelling & after ion gel activation by eye will have viscosity of from about 50-50,000 mPas.[24]

Isotonocity evaluation:

Isotonicity is important characteristics of ophthalmic preparation. Isotonicity is maintained to prevent tissue damage or irritation of eye. All ophthalmic preparation are subjected to isotonicity testing, science they exhibited good release characteristics & gelling capacity & the requite velocity. Formulation mixed with few drops of blood & observed under microscope at 45x magnification & compared with standard marketed ophthalmic formulation.[25]

Swelling studies:

Swelling studies are conducted with a cell, equipped with thermo jacket to maintain a constant temperature. The cell contains artificial tear fluid .(composition – 0.67g NaCl , 0.20g $NaHCO_3$, 0.008g $CaCl_2.2H_2O$ & distilled water q.s to 100g).swelling medium equilibrating at 37^0c one milliliter of formulated solution is placed in dialysis bag & put into the swelling medium . At specific time interval the bag is removed from the medium & weight is recorded. The swelling of the polymer gel as a function of time is determined by using the following relationship.[26,27]

$\%St = (W_t – W_0)100/W_0$

Where,

S_t= Swelling at time t.

W_0=Initial weight of gelling solution.

W_t =Final weight of gel

High Performance Liquid Chromatography:

The HPLC system is used in reversed phase mode. Analysis is performed on a Nova pack C18 packed column (150 mm length X 3.9 mm i.d).[28]

Fourier transform infra-red spectroscopy and thermal analysis:

The possibility of drug excipient interaction is investigated by FTIR studies. The FTIR graph of pure drug & combination of drug with excipient are recorded by using KBr pellets. [29]

In vitro drug release studies:

In vitro release study of in situ gel solution is carried out by using Franz diffusion cell. The formulation is placed in donor compartment & freshly prepared simulated tear fluid in receptor compartment. Between receptor & donor compartment dialysis membrane is placed (0.22 µm pore size). The whole assembly is placed on thermostatically controlled magnetic stirrer. The temperature of the medium is maintained at 37°C±0.5°C. 1ml sample is withdrawn at predetermined time interval of 1hr for 6hrs the sample volume of fresh medium is replaced. The withdrawn sample is diluted to 10ml in volumetric flask with respective solvent & analyzed by UV spectrophotometer at respective nm using reagent blank. The drug content calculated using an equation generated from standard calibration curve. The percentage cumulative drug release (% CDR) calculated. The obtained data is further subjected to curve fitting for drug release data. The best fit model is checked for Krosmeyers peppas & Fickinian diffusion mechanism for their kinetics.[30]

Ocular irritation studies-Draize Test:

Ocular irritation studies were performed on four male albino rabbits each weighing 2-3 kg. The sterile formulations were instilled twice a day for a period of 21 days and rabbits were observed periodically for redness, swelling in eye.

Albino rabbit (e.g. Newzeland white rabbit) are used as test species. One eye (e.g., right eye) is designated the test eye; the contralateral eye serves as a matched control and is usually left untreated. Single drop approximately 0.04 ml is instilled into the lower conjunctival cul-de-sac; normal blinking is allowed, although the eyelids can be held together for several seconds after instillation. Observations were done at 1, 24, 48, 72 hours one week after exposure. Ocular changes were graded by a scoring system that includes rating any alterations to the eyelids, conjunctiva, cornea, and iris**.** **[31]**

Antimicrobial activity:

Antimicrobial efficiency studies were carried out to ascertain the biological activity of sol-to-gel systems against microorganisms. This was

determined in the agar diffusion medium employing Cup plate technique. Sterile solution of marketed eye drops was used as a standard. The standard solution and the developed formulations (test solution) were taken into separate cups bored into sterile Agar previously seeded with organisms (Staphylococcus aureus and Pseudomonas aeruginosa). After allowing diffusion of solutions for two hours, the plates were incubated for 24 hrs at 37 0C. The zone of inhibition (ZOI) was compared with that of the standard. Each sample was tested in triplicate. [32, 33]

Sterility testing:

Direct inoculation method:

Preparation should be examined during usage. Sterile media was pipette out by sterile pipette and with sterile syringe then aseptically transferred the specified volume of sample to fluid thioglycolate medium and Soyabean casein digest medium and incubate for 7 days at 30 to 35^0C for fluid thioglycolate medium and 20 to 25^0C for Soyabean casein digest medium15 and periodic observation were carried upto seven days to check growth of microorganism.[33]

Accelerated stability studies:

Accelerated stability study Short term accelerated stability study was carried out for the period of 45 days for the formulations. The samples were stored at different storage conditions of room temperature, elevated temperature such as 400C at 75% RH and refrigerator (2 to 80^0c). Samples was withdrawn on weakly interval and analyzed for visual appearance, clarity, pH and drug content.[34]

CONCLUSION:

Conventional ophthalmic formulations are found to be insufficient for their activity because of less retention time of the formulation in ocular cavity. Less than 10% of the administered dose could cross the membrane. To satisfy the need, novel formulation with In-situ gelling technique came in the picture.

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